Amendments to the Drawings:

The attached sheet of drawings includes changes to Fig. 1. This sheet replaces the original sheet including Fig. 1.

REMARKS/ARGUMENTS

Claims 1 to 6 are pending in this application. Claims 1, 3, 4, 5 and 6 are amended herein. Basis for these amendments is found throughout the specification and claims as originally filed. No new matter has been added.

A replacement sheet for Fig. 1, which labels the T7 protein as SEQ ID NO: 3, and the memapsin 2T1 and 2T2 contructs as SEQ ID NOS: 32-34, is attached after page 14.

Applicants acknowledge the allowance of the claim to priority of the present application to U.S. Provisional Application Serial No. 60/178,368, filed on January 27, 2000; and to U.S. Provisional Application Serial No. 60/210,292, filed on June 8, 2000.

Compliance with Sequence Rules

The Action has objected to specification as allegedly not complying with the requirements of 37 C.F.R. §1.821 through 1.825, for reciting amino acid sequences of memapsin 2 polypeptides in Figure 1, without their SEQ ID NO identification; and for reciting linear residues of crystallized memapsin 2 protein in Table 2, without indicating what linear residues of the protein are actually represented in the crystal.

As amended herein, Figure 1 includes the amino acid sequences of the memapsin 2 polypeptides; and Table 7 indicates that the residues 1-488 of SEQ ID NO: 2, are represented in the crystallized memapsin 2 protein. Applicants request reconsideration and removal of these objections.

Specification

The Abstract

The Action has objected to the Abstract as allegedly being to long, i.e., it exceeds 150 words, and suggests that the Abstract be narrowed to a more precise summary directed to the instant invention (see, MPEP 608.01(b)).

As amended herein, the Abstract does not exceed 150 words and provides a concise summary of the invention. Applicants request reconsideration and removal of this objection.

The Drawings

The Action has objected to the descriptions for Figures 6, 7 and 9 under the Brief Description to the Drawings, as allegedly not being consistent with the actual drawings because the description references colors to distinguish various features of the drawings whereas the drawings are in black and white.

As amended herein, the descriptions for Figures 6, 7 and 9 under the Brief Description to the Drawings, are consistent with the actual drawings in Figures 6, 7 and 9. Applicants request reconsideration and removal of these objections.

Claim Objections

Claim 1

The Action has objected to claim 1 as allegedly not being clear for omitting the term "SEQ ID NO: 28" along with the general name of compound "OM-99-2." As amended herein, claim 1 includes the term "SEQ ID NO: 28" along with "OM-99-2" which renders the objection to this claim moot.

The Action has also objected to claim 1 as allegedly not being grammatically correct for reciting the terms "an K_i" instead of "a K_i." As amended herein, claim 1 recites the grammatically correct term "a K_i" which renders the objection to this claim moot.

Claim 3

The Action has objected to claim 3 as allegedly not being clear for omitting the term "β-amyloid precursor protein" in the first instance that the acronym "APP" appears.

As amended herein, claim 3 includes the terms "β-amyloid precursor protein (APP)" which renders the objection to this claim moot.

Claim 6

The Action has objected to claim 6 for reciting the terms "crystallization coordinates of memapsin 2" which are allegedly contrary to the art-accepted terminology "three-

dimensional structural coordinates..." for the description of a protein's three-dimensional structure.

As amended herein, claim 6 includes the art-accepted terminology "three-dimensional structural coordinates" instead of the terms "crystallization coordinates" which renders the objection to this claim moot.

Applicants request reconsideration and removal of these claim objections.

Claim Rejections - 35 U.S.C. §112, 2nd Paragraph

Claims 1 to 6

The Action has rejected claims 1 to 6 under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for claiming a method for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering an inhibitor to an individual, i.e., any random patient, instead of to an "individual in need thereof."

As amended herein, claims 1 to 6 are directed to a method for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease by administering to the "individual in need thereof..." which renders the rejection to these claims moot.

Claims 4 to 6

The Action has rejected claims 4 to 6 under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for claiming the method of claim 1, wherein there are allegedly two different and very distinct inhibitors described.

As amended herein, claims 4 to 6 are directed to "the method of claim 1, wherein the inhibitor of memapsin 2 which binds to the crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2 (SEQ ID NO: 28)" which renders the rejection to these claims moot.

Applicants request reconsideration and removal of these claim rejections.

Claim Rejections - 35 U.S.C. §112, 1st Paragraph

The Action has rejected claims 1 to 6 under 35 U.S.C. §112, 1st paragraph, because the specification, while being enabling for the inhibitors OM-99-1 and OM-99-2 (SEQ ID NO: 27 and 28, respectively), allegedly does not provide enablement for any inhibitor that interacts with the crystal of memapsin 2. The Action has also rejected claims 1 to 6 under 35 U.S.C. §112, 1st paragraph, because the specification allegedly fails to comply with the written description requirement. Applicants respectfully disagree.

Applicants submit that the specification provides an enabling disclosure and written description of the claimed invention. As explained below, the specification fully supports and provides guidance for one of skill in the art to make and use the claimed invention without undue experimentation and provides adequate written description of the claimed invention so as to reasonably convey to one of skill in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at paragraph [0018], the specification describes methods which have been developed for the production of purified, catalytically active, recombinant memapsin 2. The specification also states that the substrate and subsite specificity of the catalytically active enzyme have been determined, and that the active enzyme and assays for catalytic activity are useful in screening libraries for inhibitors of the enzyme.

Then, at paragraph [0019], the specification recites that the substrate and subsite specificity information was used to design substrate analogs of the natural memapsin 2 substrate, which can inhibit the function of memapsin 2. Further, the specification states that these substrate analogs are based on peptide sequences, shown to be related to the natural peptide substrates for memapsin 2, and contain at least one analog of an amide (peptide) bond which is not capable of being cleaved by memapsin 2. The specification also describes processes for the synthesis of two substrate analogues, including isosteres at the sites of the critical amino acid residues, and that the substrate analogues, OMR99-1 and OM99-2, were synthesized. The specification further explains that OM99-2, which is based on an octapeptide Glu-Val-Asn-Leu-Ala-Ala-Glu-Phe (SEQ ID NO:28) with the Leu-Ala peptide bond substituted by a transition-

state isostere hydroxyethylene group, has an inhibition constant of $1.6x10^{-9}$ M against recombinant pro-memapsin 2, and that crystallography of memapsin 2 bound to this inhibitor was used to determine the three dimensional structure of the protein, as well as the importance of the various residues in binding.

Further, at paragraph [0020], the specification states that this information can be used by those skilled in the art to design new inhibitors, using commercially available software programs and techniques familiar to those in organic chemistry and enzymology, to design new inhibitors. The specification then explains that, for example, the side chains of the inhibitors may be modified to produce stronger interactions (through hydrogen bonding, hydrophobic interaction, charge interaction and/or van der Waals interaction) in order to increase inhibition potency. Based on this type of information, the residues with minor interactions may be eliminated from the new inhibitor design to decrease the molecular weight of the inhibitor. The side chains with no structural hindrance from the enzyme may be cross-linked to lock in the effective inhibitor conformation.

Moreover, at paragraphs [0053] to [0065], the specification describes in detail, the design and synthesis of inhibitors of memapsin 2, including a description of the five human aspartic proteases, their amino acid sequences and three-dimensional structures; that typically the side chains of the amino acids are involved in the specificity of the substrate/aspartic protease interaction; that while there is a general motif for aspartic protease substrate recognition, each protease has a very different substrate specificity and breadth of specificity; that the information on the specificity of an aspartic protease can be used to design specific inhibitors in which the preferred residues are placed at specific sub-sites and the cleaved peptide bond is replaced by an analog of the transition-state, i.e., a transition state isostere; a discussion on transition state theory and that a typical transition-state isostere of aspartic protease is hydroxyethylene group, i.e., -CH(OH)-CH_2-; a description of substrate analog compositions; and preferred side chains of small peptide molecules.

As explained above, the specification provides sufficient guidance and written description to enable one of skill in the art to make and use the claimed invention without undue

experimentation, and reasonably conveys to one of skill in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants request reconsideration and removal of these rejections.

Claim Rejections - 35 U.S.C. §102 and 35 U.S.C. §103

The Action has rejected claims 1 to 3 under 35 U.S.C. §102(a) as allegedly being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as allegedly being obvious over Shina *et al.* (Nature, 2 December 1999, 402: 537-540). Applicants respectfully disagree.

As amended herein, claims 1 to 3 distinguishes over Shina *et al.* by claiming methods for treating a patient to decrease the likelihood of developing or the progression of Alzheimer's disease, by administering to the individual in need thereof, an effective amount of an inhibitor of memapsin 2 having a **K_i of less than or equal to 10^{-7} M** or which **binds to crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2 (SEQ ID NO. 28)**.

Shina *et al.* does not disclose, teach or suggest any such methods. Instead, this reference discloses purification and cloning of amyloid precursor protein β-secretase from human brain, wherein a P_{10}-$P_{4'}$, P_1-(S)-statine substituted substrate analogue dose-dependently inhibited the soluble β-cleavage activity with half-maximal inhibitory concentration (IC_{50})~40 μM. This reference does not disclose, teach or suggest any methods for treating Alzheimer's disease by administering an effective amount of an inhibitor of memapsin 2 having a K_i of less than or equal to 10^{-7} M or which binds to the crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2 (SEQ ID NO. 28) as required by the instant claims. Absent a teaching or suggestion in the cited reference, one of skill in the art would not have been motivated to do what applicants now claim.

Nor would there be any reasonable expectation of success in reaching the claimed invention based on the teachings of Shina *et al.* As discussed above, this reference teaches that a P_{10}-$P_{4'}$, P_1-(S)-statine substituted substrate analogue dose-dependently inhibited the soluble β-cleavage activity with half-maximal inhibitory concentration (IC_{50})~40 μM. This reference does

not teach or suggest any methods or inhibitors of memapsin 2 having a K_i of less than or equal to 10^{-7} M or which binds to the crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2 (SEQ ID NO. 28) as required by the instant claims. Indeed, this reference does not disclose, teach or suggest any inhibitors which bind to the crystallized memapsin 2. Thus, one of skill in the art would not have any reasonable expectation of success in reaching the claimed invention based on the teachings of Sinha *et al.*

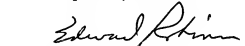
Nor do the teachings of Brandon and Tooze cure the defects of Sinha *et al.* because this reference does not teach or suggest any methods or inhibitors of memapsin 2 having a K_i of less than or equal to 10^{-7} M or which binds to the crystallized enzyme characterized by the parameters in Table 2 when bound to OM-99-2 (SEQ ID NO. 28) as required by the instant claims. Instead, this reference teaches that "well-ordered crystals are difficult to grow, because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules"; and that "these channels, which usually occupy more than half the volume of the crystal, are filled with disordered solvent molecules" (see, page 270). Thus, the claimed invention is not obvious over the teachings of Sinha et al. in view of Brandon and Tooze. Applicants request reconsideration and removal of these rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6155.

Respectfully submitted,



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Attachments
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